Food allergy and eosinophilic gastrointestinal disorders

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ABSTRACT

Eosinophilic esophagitis (EoE) is a non–immunoglobulin E mediated disorder that has been seen with increasing frequency over the past 25 years. Although the presentation varies per age group from vomiting and refusal to eat in infants and toddlers to abdominal pain and dysphagia in school-aged children, and food impaction and indigestion in adolescents and adults. Treatment options include proton-pump inhibitors, dietary avoidance, swallowed steroids, or a combination of these. Newer therapies with biologics show promise in early studies. Cow's milk is the most common food trigger of EoE across all age groups, followed by wheat and eggs. Different dietary avoidance strategies have been used, and help from a knowledgeable nutritionist is often key to success. Patients with EoE commonly have other baseline atopic disease. Clinicians who take care of patients who are atopic, therefore, should have a higher index of suspicion for EoE in patients with dysphagia. The goals of treatment are both a decrease in symptoms and normalization of esophageal histology. Eosinophilic gastrointestinal diseases are less common and less likely to respond to dietary therapies and/or avoidance. Pathogenesis seems to be different and may be more autoimmune mediated. Trialing dietary restrictions is certainly an option in this cohort of patients. For persistent symptoms and abnormalities, systemic medications have been used, although biologics may be used in the future. Additional studies are needed to determine which patients will respond to which therapies.

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Eosinophilic gastrointestinal diseases (EGID) are a constellation of diseases with eosinophilic inflammation in the gastrointestinal (GI) tract, divided based on the location of the eosinophils. Eosinophilic esophagitis (EoE) involves eosinophils isolated to the esophagus, eosinophilic gastritis (EG) has eosinophils in the stomach, eosinophilic colitis (EC) has eosinophilic infiltration in the colon, and eosinophilic gastroenteritis (EGE) has eosinophils throughout the GI tract (reviewed by Egan and Furuta[1]).

EoE is the most common EGID, with an estimated prevalence of 1/2000.[2] The symptoms of EoE vary with age of presentation.[3] Infants often present with vomiting, feeding disorders, and failure to thrive. School-aged children can present with vomiting, epigastric abdominal pain, and other symptoms of gastroesophageal reflux disease (GERD). Adolescents and adults typically present with acute and/or chronic dysphagia, esophageal narrowing and food impaction. GERD symptoms (heartburn) may occur but are not typical. Patients can be underweight, normal weight, or overweight.

EoE is seen more commonly in individuals with underlying atopic conditions, such as asthma, allergic rhinitis, immunoglobulin E (IgE) mediated food allergy, and atopic dermatitis.[4] The rate of EoE is 10-fold higher in patients with IgE-mediated food allergy compared with the general population.[5] The diagnosis of EoE is made by an upper endoscopy with biopsy. Classic visual findings on endoscopy include esophageal furrowing, narrowing, rings, and white plaques, but the mucosa may also seem normal in 25% of patients, which stresses the importance of obtaining a biopsy of the tissue. If esophageal biopsy specimens have >15 eosinophils per high power field in any field, EoE can be diagnosed after other causes of eosinophilia are excluded (infection, drug reaction).[3]

Unlike IgE-mediated food allergy to milk, wheat, and soy, in which it is outgrown in 60–90% of patients[6] or to food protein–induced enterocolitis[7], EoE is almost never outgrown, with a resolution rate of outgrowing all foods at <3% and for individual foods at <10%, which is closer to a peanut IgE–mediated food allergy.

There are three basic treatment options for EoE: proton-pump inhibitors (PPI), dietary therapy, swallowed topical steroids, or a combination of these options. Primarily in the adult population, intermittent dilations have been used to improve strictures and/or narrowing, but this therapy does not treat underlying inflammation and is a temporizing measure. Choosing

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between these therapies is highly individualized and dependent on lifestyle, quality of life, and adherence. There are also individual patients in whom more than one different modality has been successful in treating EoE, *e.g.,* PPI or diet therapy, which led to resolution of esophageal eosinophilia in the same patient.[8]

PPIs

PPIs can result in resolution of esophageal eosinophilia in up to 50% of patients. These medications may work by directly decreasing inflammation or improving GERD or both in the same patient. In our center, 37% of children with a diagnosis of EoE and unresponsive to therapy with diet or steroids had a complete or near-complete response when treated with a PPI.[9] This demonstrates that PPIs are not always interchangeable with other treatments for EoE and sometimes are only treating GERD.

DIETARY THERAPY

EoE is considered a food allergy that meets a Koch postulate, *i.e.,* when a specific food(s) is eliminated, there is improvement in symptoms and normalization of biopsy specimens, and, when added back, symptoms and biopsy abnormalities return. In both pediatric and adult cases, >95% of patients will respond, with normalization of histology and symptoms when treated with an elemental diet, and symptoms and eosinophils reoccur when food is reintroduced. The biggest challenge is in identifying the causative food(s) in EoE because the mechanism is non-IgE mediated. Therefore, when selecting a diet therapy, there are multiple options, which range from a single-food elimination (primarily cow's milk), two-food elimination (cow's milk and wheat or cow's milk and egg), multiple-food elimination (four- or six-food group elimination diets or an elemental diet), or partial or full use of amino acid–based formulas.[10] When considering dietary avoidance, including a registered dietician and/or nutritionist well versed in EoE is important to ensure adequate growth in children and proper micro- and macronutrient intake for patients of any age. A registered dietician can also help in designing a diet that is nutrition balanced for calories and proteins for each individual patient.

The most-effective treatment is removal of all foods, which necessitates an elemental diet, which primarily consists of an amino acid–based formula. On meta-analysis, elemental diets resulted in remission rates of >90% in both children and adults.[11] However, this diet can be expensive and adherence can be difficult and next to impossible for adults and older children. Therefore, various empiric and testing-based diet therapies have been used. In targeted therapy, foods are eliminated based on allergy testing. However, EoE is a non–IgE-mediated disease because standard skin testing or specific IgE testing is not predictive of a response to a food elimination trial. In addition, omalizumab (anti-IgE) has no effect on disease because IgE blockade of IgE-mediated adverse events is one of the effects seen in oral immunotherapy (OIT) and subcutaneous immunotherapy.[12] Elimination diets by using atopy patch testing have been tried with some success (50%), depending on the center that uses the test and the age group of the patient.[13] Nevertheless, skin testing has a role because many patients have IgE-mediated food allergy to other foods, *e.g.,* anaphylaxis to peanut and EoE to cow's milk.[4]

In addition, there have been rare cases when patients re-introduced a food removed for treatment of EoE; the same patients develop immediate IgE-mediated symptoms. These patients have both IgE-mediated allergy and EoE to the same food, and, by taking it every day, they are desensitized to the food but it causes EoE. In our experience, we have seen this in <1 per 100 patients. But, for these instances, skin testing before reintroduction may have a role.[14,15] The other circumstance in which patients can have IgE and non-IgE reactions to the same food is seen in OIT. OIT can induce EoE in 5–20% of the patients. The symptoms may occur early or late in the course of treatment. In these patients, OIT is treating the IgE-mediated allergy but induces EoE because these patient have both IgE and EoE to the same food.[16]

The third option is empiric elimination. The most notable is the six-food group elimination diet, which eliminates all products that contain cow's milk, wheat, egg, soy, peanut, and tree nut as well as fish and shellfish. In addition, depending on the study, the "six-food groups" varied per study because some patients avoided wheat and others avoided grains (gluten, including wheat, oat, and rice). Response rates to six-food group elimination diet are varied, with response rates of 50–70%, depending on the study and the population.[11] Subsequent studies found that most EoE cases are triggered by one to three foods, with cow's milk, egg, and wheat being the most common. Therefore, simpler empiric two- and four-food diet eliminations have been tried with similar success rates and with easier complaince.[17]

ENVIRONMENTAL ALLERGY IMMUNOTHERAPY

EoE can be triggered by environmental allergies by either seasonal and indoor allergens in ~10% of the patients.[18] Evidence that seasonal allergies can exacerbate their EoE is seen in individual patients,[18] case reports, and seasonality of a diagnosis of EoE. EoE has also been reported to be treated with allergy immunotherapy to pollens[18] and indoor allergens. In these

patients, percutaneous skin testing to aeroallergens is necessary for a diagnosis.

TOPICAL CORTICOSTEROID

Another treatment option for EoE is a swallowed topical steroid preparation that uses medications typically used to treat asthma. Nebulized budesonide made into a slurry or an aerosolized fluticasone (used without a spacer) induces remission in 50–90% of patients, with a reduction in symptoms, mucosal inflammation, and eosinophil counts.[3] After administration of these medications, patients must avoid eating, drinking, rinsing their mouth, or brushing their teeth for 30 minutes. Although these medications allow most patients to continue unrestricted diets, potential adverse effects include growth suppression and esophageal candida (treatable but not preventable). This therapy is currently not approved by the U.S. Food and Drug Administration for the treatment of EoE, but, nonetheless, it is a mainstay of medical management.

Swallowed budesonide and swallowed fluticasone propionate are the two formulations used for EoE because they have been the most studied. Budesonide vials can be mixed with five packets of sucralose to create a viscous slurry that can be swallowed. Small volumes (1 teaspoon) of applesauce, honey, or similar thickening agents can be used as an alternative vehicle.[19] Fluticasone propionate should be swallowed from the inhaler directly without a spacer, with dosing from 2 puffs of 110 μg twice daily to 4 puffs of 220 μg twice daily, depending on age and response.[10,20]

BIOLOGICS

Newer therapies that target the pathways that lead to eosinophilic inflammation are in clinical trials, including agents against interleukin (IL) 5, IL-4 receptor, IL-13, IL-5 receptor, and Sialic acid-binding immunoglobulin-type lectins (siglec)-8.[10,21] In the most successful trial to date, 61% of adult patients had normal endoscopies (<6 eosinophils/high power field) after receiving 12 weeks of dupilumab (anti–IL-4 receptor antagonist that blocks anti–IL-4 and anti–IL-13).[22] Similar trials in adolescents and children have begun. Based on these promising results, biologics against T-helper type 2 cytokines are currently in phase III clinical trials to verify these results in the treatment of EoE and EG.

COMBINATION THERAPY

In many patients in whom single therapies do not work or they do not want a very restrictive diet, combination of therapies (diet, PPI, and swallowed steroids) have led to improvement in symptoms and histology.

MONITORING FOR EoE

In EoE, the goal of treatment is twofold: to reduce symptoms and to prevent long-term esophageal damage and fibrosis that is seen in adults due to abnormal inflammation.[23] Unfortunately, symptoms do not always correlate with histology. There are patients who remain symptomatic and have normal histology (which necessitates evaluation for concomitant disorders). There are also patients who become asymptomatic but who have abnormal biopsy specimens. Many times, patients adopt modifying behaviors to decrease symptoms, such as avoiding meats or bread, drinking more with meals, or cutting food into smaller bites.[24] Therefore, it is important that, when therapies are modified, an endoscopy is performed to ensure that histologic remission has been maintained.

OTHER EGIDs AND FOOD ALLERGY

EG causes upper-GI symptoms, including abdominal pain, vomiting, and failure to gain weight. EGE typically involves the stomach and small bowel, and can cause both upper and lower intestinal symptoms. Eosinophils may be elevated in the colon in EC, and the typical symptom is diarrhea. These EGIDs are rarer than EoE as EG, EGE, and EC have a reported prevalence of 6.3, 8.4, and 3.3 per 100,000 people, respectively.[25]

The role of food allergy for non-EoE EGIDs are less clear. EG has been shown to be responsive to cow's milk elimination in some populations[26,27] but not all.[28] In a meta-analysis, 86 patients with EG were given either an elemental or hydrolyzed protein formula, or were advised to follow the six- or seven-food elimination diet. Sixty-eight patients (79%) demonstrated clinical improvement, and 16 of 20 patients (80%) who had follow-up biopsies had histologic improvement or remission.[29] The amount of improvement is not clear. Therefore, the improvement may be due to changes in the diet or to the autoimmune process improving on its own. Case reports of EC have indicated a response to diet.[30–32] However, the number of patients in all of these cases is relatively small. In infants, EC has been shown to be responsive to cow's milk,[33] which might represent a different population than in adults in whom EC is more likely an early sign of inflammatory bowel disease.[34]

CONCLUSION

EoE is a non–IgE-mediated complex disorder of esophageal mucosal inflammation. The diagnosis of EoE relies on an accurate histopathologic diagnosis by using biopsy specimens obtained *via* endoscopy. EoE is a food-driven disease, but it is not a classic IgE-mediated disease. Traditional skin-prick or specific IgE testing does not reveal causative food, and anti-IgE

therapies do not work. Therefore, dietary therapies are primarily based on empiric food elimination. Cow's milk is one of the causes in 70% of cases and the sole cause of disease in 30% of cases. Patients who have outgrown an individual food allergy or who are undergoing OIT to a food can get EoE to the same food, which indicates two different mechanisms. Alternative medical therapies for EoE include PPIs, swallowed corticosteroids, or, in the future, biologics.

Patients with EoE are at higher risk of having other comorbid atopic diseases, including asthma, allergic rhinitis, atopic dermatitis, and a 10-fold increase in IgE-mediated food allergy. Monitoring for EGIDs in this atopic population is critical. For non–esophageal EGIDs, case series and abstracts indicate that food allergy may play role.[27–28,30–33] Therefore, treatment with dietary therapy can be considered. However, patients do not respond to diet and seem to have a more autoimmune pathogenesis. Therefore, additional research is needed in the treatment of EGIDs. Patients with EoE have an increased risk of IgE-mediated food allergy (hives, anaphylaxis), so evaluation of food allergy is critical in EoE. For other non-EoE EGIDs, diet may play a role and dietary therapy should be considered; however, the data are limited and not as well controlled for determining the optimal diet.

KEY POINTS

- Symptoms of esophageal dysfunction vary by age and should raise concern for EoE.
- A diagnosis of EoE should be made when symptoms of esophageal dysfunction are present and esophageal biopsy confirms at least 15 eosinophils per high powered field on biopsy specimen in the absence of additional disorders, which could cause esophageal eosinophilia.
- Some patients with EoE may be managed successfully when using PPI, dietary exclusion, or swallowed steroid as monotherapy. However, some patients may benefit from a combination of modalities.
- Cow's milk, egg, and wheat are the most common foods that trigger EoE.
- Other EGIDs are less typically food driven, but dietary therapy can be trialed.
- Future therapies may include the use of biologics.
- Patients can have both IgE (urticaria) and non-IgE (EoE) reactions to the same food.

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